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Original article

Extracellular Volume Detects Amyloidotic Cardiomyopathy and Correlates With Neurological Impairment in Transthyretin-familial Amyloidosis

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ABSTRACT

Introduction and objectives: Cardiac involvement determines prognosis and treatment options in transthyretin-familial amyloidosis. Cardiac magnetic resonance T_1 mapping techniques are useful to assess myocardial extracellular volume. This study hypothesized that myocardial extracellular volume allows identification of amyloidotic cardiomyopathy and correlates with the degree of neurological impairment in transthyretin-familial amyloidosis.

Methods: A total of 31 transthyretin-familial amyloidosis patients (19 mean age, 49 ± 12 years; 26 with the Val30Met mutation) underwent a T_1 mapping cardiac magnetic resonance study and a neurological evaluation with Neuropathy Impairment Score of the Lower Limb score, Norfolk Quality of Life questionnaire, and Karnofsky index.

Results: Five patients had cardiac amyloidosis (all confirmed by ^{99m}Tc-DPD scintigraphy). Mean extracellular volume was increased in patients with cardiac amyloidosis (0.490 ± 0.131 vs 0.289 ± 0.035; P = .026). Extracellular volume correlated with age (R = 0.467; P = .008), N-terminal pro-B-type natriuretic peptide (R_S = 0.846; $P < .001$), maximum wall thickness (R = 0.621; $P < .001$), left ventricular mass index (R = 0.685; $P < .001$), left ventricular ejection fraction (R = −0.378; P = .036), Neuropathy Impairment Score of the Lower Limb (R_S = 0.604; P = .001), Norfolk Quality of Life questionnaire (R_S = 0.529; P = .003) and Karnofsky index (R_S= −0.517; P = .004). A cutoff value of extracellular volume of 0.357 was diagnostic of cardiac amyloidosis with 100% sensitivity and specificity ($P < .001$). Extracellular volume and N-terminal pro-B-type natriuretic peptide were the only cardiac parameters that significantly correlated with neurologic scores.

Conclusions: Extracellular volume quantification allows identification of cardiac amyloidosis and correlates with the degree of neurological impairment in transthyretin-familial amyloidosis. This noninvasive technique could be a useful tool for early diagnosis of cardiac amyloidosis and to track cardiac and extracardiac amyloid disease.

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El volumen extracelular detecta la amiloidosis cardiaca y está correlacionado con el deterioro neurológico en la amiloidosis familiar relacionada con la transtiretina

Palabras clave:
Amiloide
Transtiretina
Resonancia magnética cardiaca
Volumen cardiaco extracelular
Mapeo T_1

RESUMEN

Introducción y objetivos: La afección cardiaca determina el pronóstico y las opciones de tratamiento en la amiloidosis familiar relacionada con la transtiretina. Las técnicas de mapeo T_1 de resonancia magnética cardiaca son útiles para determinar el volumen extracelular miocárdico. En este estudio se planteó la hipótesis de que el volumen extracelular miocárdico permite la identificación de la amiloidosis cardiaca y está correlacionado con el grado de deterioro neurológico en la amiloidosis familiar relacionada con la transtiretina.

Métodos: A un total de 31 pacientes con amiloidosis familiar relacionada con la transtiretina (19 varones; media de edad, 49 ± 12 años; 26 pacientes con la mutación Val30Met), se les realizaron estudios de mapeo T_1 con resonancia magnética cardiaca y una evaluación neurológica con la *Neuropathy Impairment Score of the Lower Limb*, el cuestionario *Norfolk Quality of Life* y el índice de Karnofsky.

Resultados: Cinco pacientes tenían amiloidosis cardiaca (en todos los casos, confirmada mediante gammagrafía con ^{99m}Tc-DPD). El valor medio del volumen extracelular estaba aumentado en los pacientes con amiloidosis cardiaca (0,490 ± 0,131 frente a 0,289 ± 0,035; p = 0,026). El volumen extracelular mostró correlación con la edad (R = 0,467; p = 0,008), fracción aminoterminal del propéptido natriurético tipo B (R_s = 0,846; p < 0,001), el grosor máximo de la pared (R = 0,621; p < 0,001), el índice de masa ventricular izquierda (R = 0,685; p < 0,001), la fracción de eyección del ventrículo izquierdo (R = –0,378; p = 0,036), la puntuación de la *Neuropathy Impairment Score of the Lower Limb* (R_s = 0,604; p < 0,001), el cuestionario *Norfolk-Quality of Life* (R_s = 0,529; p = 0,003) y el índice de Karnofsky (R_s = –0,517; p = 0,004). Se consideró que un valor de corte del volumen extracelular de 0,357 es diagnóstico de amiloidosis cardiaca con sensibilidad y especificidad del 100% (p < 0,001). El volumen extracelular y la fracción aminoterminal del propéptido natriurético tipo B son los únicos parámetros cardiacos que mostraron correlación significativa con las puntuaciones neurológicas.

Conclusiones: La cuantificación del volumen extracelular permite la identificación de la amiloidosis cardiaca y está correlacionada con el grado de deterioro neurológico en la amiloidosis familiar relacionada con la transtiretina. Esta técnica no invasiva puede ser un instrumento útil para el diagnóstico precoz de amiloidosis cardiaca y el seguimiento de la afección cardiaca y extracardiaca.

Abbreviations

AC: amyloidotic cardiomyopathy
CMR: cardiac magnetic resonance
ECV: extracellular volume
FAP: familial amyloid polyneuropathy
TTR: transthyretin

INTRODUCTION

Transthyretin (TTR) familial amyloidosis, also known as familial amyloid polyneuropathy (TTR-FAP), is an autosomal dominant inherited disorder caused by mutations in the TTR gene.[1]

In this disorder, mutated TTR protein precipitates as extracellular amyloid deposits, mainly in peripheral nerves and in the heart.[1,2] Although neurological impairment usually dominates clinical manifestations, heart involvement frequently determines the prognosis.[2–4]

Available treatments for TTR-FAP include liver transplantation[5] and the TTR stabilizer tafamidis.[6] Several other compounds are under investigation with promising initial results.[7] Currently, it is recommended to start drug therapy or proceed with liver transplantation when the first signs and symptoms of neurological impairment are identified.[8,9]

Unfortunately, when the first symptoms appear, amyloid deposits could be large enough to compromise the patient's clinical course thereafter. Methods to detect early amyloid deposits are therefore needed. Moreover, a method that quantifies the amount of amyloid in the tissues over time would be desirable to monitor treatment response and to establish a cutoff point to start treatment.[2]

Amyloidotic cardiomyopathy (AC) is one of the leading causes of death in TTR-FAP patients[2,3,5] and a significant number of TTR-FAP patients have underdetected cardiac involvement.[2,10]

The definitive diagnosis of AC requires histological evidence of amyloid deposits[2–4]; however, endomyocardial biopsy has associated risks and a noninvasive diagnostic approach with imaging techniques is commonly preferred. In patients with genetically confirmed TTR-FAP, AC is accepted in cases of unexplained increased ventricular thickness/mass and typical findings of AC either on ^{99m}TC-DPD scintigraphy or on cardiac magnetic resonance (CMR).[2,8,11]

T_1 mapping CMR techniques allow, through a simple equation, an estimate of the heart volume occupied by extracellular components.[12,13] As TTR amyloid deposits are extracellular, cardiac extracellular volume (ECV) value reflects the amount of TTR amyloid deposits in the myocardium and could serve as a tool to diagnose AC and to monitor its progression.[13,14] Furthermore, cardiac ECV could reflect the amount of amyloid deposits that are present in other tissues.

The purpose of this study was 2-fold: to determine if increased ECV allows the identification of AC in TTR-FAP patients, and to explore if cardiac ECV correlates with the degree of neurological impairment caused by TTR amyloid extracardiac deposits.

METHODS

Study Population

After approval from the institutional review board, 31 genetically proven TTR-FAP participants (19 men; mean age,